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Staphylococcal Exopolysaccharides Inhibit Lymphocyte Proliferative Responses by Activation of Monocyte Prostaglandin Production

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The glycocalyx (exopolysaccharides) of *Staphylococcus epidermidis* has been reported to inhibit a variety of host defense mechanisms. We have examined the inhibitory effects of glycocalyx on the proliferation of human peripheral blood mononuclear cells (PBMC) and the mechanism of this inhibition. Glycocalyx isolated and partially purified under endotoxin-free conditions from defined liquid medium cultures of *S. epidermidis* and *Staphylococcus lugdunensis* inhibited the proliferative response of PBMC when added to cultures at 10 to 100 μg/ml. Glycocalyx-mediated inhibition of phytohemagglutinin-stimulated proliferation of PBMC required the presence of plastic-adherent peripheral blood monocytes. Culture supernatants of monocytes stimulated with glycocalyx contained a soluble factor that inhibited the proliferation of monocyte-depleted PBMC. This soluble inhibitory factor was not produced in the absence of glycocalyx or in the presence of both glycocalyx and indomethacin. Analysis of the supernatants of cultures of adherent monocytes revealed that glycocalyx from *S. epidermidis* and from *S. lugdunensis* could activate monocyte production of prostaglandin E_2 (PGE_2), human interleukin-1, and tumor necrosis factor alpha. The addition of purified PGE_2, at the same levels of PGE_2 ($\geq 10^{-9}$ M) generated in the monocyte cultures, to PBMC cultures resulted in a similar inhibition of proliferative responses. It is concluded that, contrary to previous suggestions, the bacterial glycocalyx does not have a direct inhibitory effect on T lymphocytes. However, it does appear that glycocalyx from coagulase-negative staphylococci can activate monocyte PGE_2 production and that it is this activity that in turn contributes to the inhibition of T-cell proliferation.

The bacterial glycocalyx may be found attached to the bacterial cell, forming the capsule, or detached from the cell, forming the bacterial slime (14, 20, 31, 36). Bacteria adhere to surfaces and form biofilms composed of bacterial cells and glycocalyx (11, 17, 31). This microcolonial form of growth has been observed in bacterial diseases including cystic fibrosis (26), prosthesis-related colonization (11, 23, 24) and infection (27), experimental animal osteomyelitis (19, 20, 28) and endocarditis (2), and human osteomyelitis (20, 25). It has been suggested by several research groups that the production of glycocalyx may be a major factor in the pathogenesis of foreign body infections (6, 15, 18, 25, 30). Glycocalyx production can protect bacteria from surfactants (12), antibodies (3), antibiotics (5), and phagocytosis (10, 16, 34, 39). Glycocalyx has been reported to inhibit normal phagocyte functions, such as movement along chemotactic gradients and oxidative burst, as well as particle engulfment (16, 30, 34, 39).

Recently, another attribute of bacterial glycocalyx that may be relevant to its role in pathogenesis of infectious diseases has been suggested by the observation that the glycocalyx from coagulase-negative staphylococci can inhibit the proliferation of human peripheral blood mononuclear cells (PBMC) stimulated with the T-cell mitogen phytohemagglutinin (PHA) (13, 30). In the present study we examined the mechanism of this inhibition to determine whether the inhibitory effect was a result of the direct action of the glycocalyx on T lymphocytes or whether the inhibition was mediated through another cell type, such as peripheral blood monocytes.

MATERIALS AND METHODS

Reagents. Prostaglandin E_2 (PGE_2) and a kit for radioimmunoassay for PGE_2 were obtained from Advanced Magnetics, Inc. (Cambridge, Mass.). E-Toxate *Limulus* assay kits for the detection of bacterial endotoxin were obtained from Sigma Chemical Co. (St. Louis, Mo.). Enzyme-linked immunosorbent assay (ELISA) kits for the detection of human interleukin-1 (IL-1β) and tumor necrosis factor alpha (TNF-α) were obtained from Cistron Biotechnology (Pine Brook, N.J.) and Endogen, Inc. (Boston, Mass.), respectively. Lipopolysaccharide (LPS; from *Escherichia coli* O11:B4-W) and indomethacin were obtained from Sigma. A 10^{-2} M solution of indomethacin in ethanol was prepared on the day of use and was diluted to the desired concentration in culture medium. The M1/70 hybridoma-producing anti-CD11a antibody was obtained from the American Type Culture Collection (Rockville, Md.). Anti-CD2 (fluorescein isothiocyanate conjugate) was obtained from Coulter Immunology (Hialeah, Fla.).

Preparation of bacterial glycocalyx. The *Staphylococcus* strains used in this study included *S. epidermidis* G-19-85, isolated from a cesarian section wound (East Tennessee State University, Johnson City), and *S. lugdunensis* G-6-87 (strain N850412 from the blood of a patient with septicemia) and G2-89 (strain CRS 307 from the blood of a patient with infective endocarditis), isolated by J. Fleurette (Laboratoire de Bactériologie-Virologie, Faculté de Médicine Alexis Carrel, Lyon, France). The glycocalyx was isolated from bac-

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TABLE 1. Characterization of bacterial glycocalyx preparations

Glycocalyx prep	Organism	Amt (per 100 μg of glycocalyx) of:			
		Endotoxin (ng)	Carbohydrate (μg)	Protein (μg)	Phosphate (nmol)
G-19-85	*S. epidermidis*	<0.1	18	64	94
G-6-87	*S. lugdunensis*	<0.1	8.3	55	67
G-2-89	*S. lugdunensis*	<0.1	5.0	66	151
G-2-89 (Westphal extracted)	*S. lugdunensis*	<0.2	9.5	14	200

teria grown in an endotoxin-free chemically defined medium. The use of defined medium is the method of choice over previously published methods (12), since it yields a more consistent product without the impurities that may be derived from nutrient agar (14). A chemically defined medium developed previously for glycocalyx production in *Bacteroides* spp. (17) was modified for growth of staphylococci as follows. $NaHCO_3$ and hemin were omitted. Individual amino acids were used at the following final amounts per liter: glutamic acid, phenylalanine, leucine, isoleucine, valine, proline, aspartic acid, glycine, lysine, arginine, asparagine, and glutamine, 1.0 mg; histidine and serine, 0.5 mg; alanine and methionine, 0.25 mg; threonine, 2.0 mg; and cysteine, 5.0 mg. These concentrations were used by van de Rijn and Kessler (38) and for the isolation of *S. epidermidis* glycocalyx (31).

Endotoxin-free glass-distilled water and glassware were used throughout the preparation and isolation procedures. Bacteria were grown for 18 h at 37°C in chemically defined medium and then centrifuged at 33,000 × *g* for 10 min. Supernatant fluid was centrifuged at 3,000 × *g* and reduced to one-third volume by using a rotary evaporator. The glycocalyx was then dialyzed (cellulose acetate dialysis tubing; molecular weight cutoff, 12,000 to 14,000) against distilled water for 5 days, centrifuged at 3,000 × *g* for 20 min, and filtered through a 0.22-μm-pore-size filter. The resulting preparation was frozen and lyophilized.

The results of the biochemical analysis of the glycocalyx preparations are displayed in Table 1. The total carbohydrate content was determined by the phenol-sulfuric acid assay of Dubois et al. (9). Total protein was estimated by the method of Lowry et al. with bovine serum albumin as the standard (22). Total phosphate was measured by the method of Ames with KH_2PO_4 as the standard (1). Endotoxin was estimated by using E-Toxate *Limulus* kits. Depletion of protein was accomplished by hot phenol extraction (41). Briefly, an equal volume of hot (70°C) phenol was added to glycocalyx suspended in distilled water at an approximate concentration of 4 mg/ml. The mixture was incubated with stirring for 60 min at 70°C, and the phenol and aqueous layers were separated by centrifugation at 20,000 × *g* for 20 min. An equal volume of water was added to the phenol layer, and incubation and centrifugation were repeated. The aqueous layers were combined, and residual phenol was removed by exhaustive dialysis against distilled water. The resulting preparation was frozen and lyophilized. A procedure control was prepared by dissolving starch in distilled water and subjecting it to the same dialysis and hot phenol extraction procedures.

Cell preparation and culture. Peripheral blood from normal donors (aged 26 to 45 years) was aseptically collected from the antecubital vein in a heparinized syringe (A. H. Robins, Richmond, Va.). The PBMC were isolated by density gradient centrifugation on Lymphoprep (Accurate Chemical and Scientific Co., Westbury, N.Y.) and then washed once with cold physiological saline and three times in cold Dulbecco phosphate-buffered saline (0.15 M, pH 7.3) supplemented with 2% (vol/vol) heat-inactivated (56°C for 60 min) fetal bovine serum (GIBCO, Grand Island, N.Y.) that had been prescreened for an endotoxin level of <50 pg/ml. The mononuclear cells were then resuspended in RPMI 1640 (GIBCO) supplemented with 5% (vol/vol) heat-inactivated fetal bovine serum, 10 mM *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (GIBCO), 1 mM pyruvate, and 50 μg of gentamicin (Sigma) per ml (henceforth referred to as complete medium) and dispensed in 0.1-ml aliquots into flat-bottom Micro-Test III plates (Falcon Plastics, Oxnard, Calif.) to a final concentration of 5×10^5 cells/ml. PHA-M (Sigma) was then added at 1 μg/ml in the presence or absence of bacterial glycocalyx. After incubation for 5 days at 37°C in a humidified atmosphere of 5% CO_2 and 95% air, the cultures were pulsed for 4 h with [^{3}H]thymidine (36) and harvested on a MASH-II harvester (M. A. Bioproducts, Walkersville, Md.). The filters were washed with distilled water, air dried, immersed in a scintillation fluid, and counted on a Beckman LS7000 scintillation spectrometer.

Monocyte depletion of PBMC. PBMC were depleted of monocytes by dispensing a 10-ml aliquot of PBMC at 2×10^6 cells per ml of complete medium to a 60-mm^2 culture dish (Falcon). After 2 to 4 h of incubation at 37°C, the nonadherent cells were gently agitated and collected. This procedure reduced the monocyte content by 5- to 10-fold from the 16 to 22% monocyte content of unseparated PBMC to 2 to 5%.

Generation of monocyte supernatants. Peripheral blood monocytes were enriched in 96-well culture plates by incubating PBMC at 2×10^6 cells per ml for 2 to 4 h and then washed three to five times to remove nonadherent cells. The adherent cells were >90% CD11a$^+$ and <2% CD2$^+$ as determined by fluorescence microscopy after labeling with the appropriate fluorescein isothiocyanate-conjugated monoclonal antibody. The adherent cells were then cultured for 1 or 2 days in the absence or presence of glycocalyx and/or indomethacin. Supernatants were collected, and the presence of a soluble inhibitory factor was determined by adding these supernatants (50%, vol/vol) to cultures of PHA-stimulated, nonadherent PBMC. The proliferation of these cultures was determined by measuring [^{3}H]thymidine incorporation as described above. Samples of these supernatants were also subjected to the radioimmunoassay for PGE_2 and to the ELISA for IL-1β and TNF-α. Bioassays for IL-1 (21) and TNF-α (8) were run to corroborate the ELISA results. Briefly, IL-1-dependent D10.G4 cells were cultured at 2×10^4 cells in 200 μl with 2 μg of concanavalin A per ml and threefold serial dilutions of the test supernatant. Proliferation was assessed by measuring [^{3}H]thymidine incorporation after 3 days of culture (21). One unit of IL-1 was defined as the amount supporting half-maximal proliferation of D10.G4 in these cultures (21). For the TNF-α bioassay, L929 fibroblasts were cultured overnight as previously described (8) with supernatants diluted 5- to 100-fold. The plates were washed, stained with crystal violet, and read on a VMAX automated plate reader at 558 nm (Molecular Devices, Menlo Park, Calif.). A standard curve generated by titration of 0.05 to 10 U of recombinant TNF-α (Genzyme Corp., Cambridge, Mass.) per ml was run in parallel for calculation of the activity in the supernatants. Anti-TNF-α antibody (Genzyme) was added to replicates of the supernatants to confirm that cytotoxicity was caused by TNF-α.

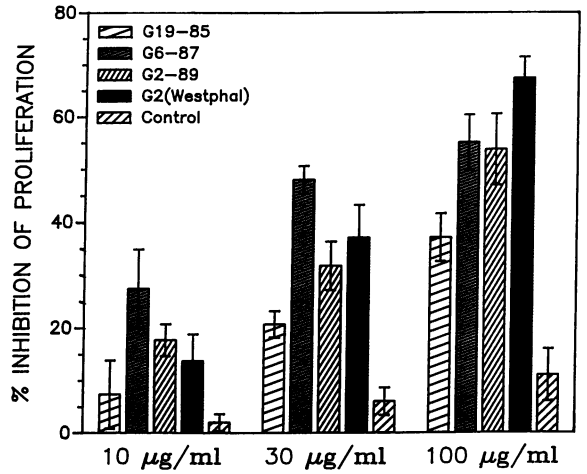

FIG. 1. Inhibition of lymphocyte proliferative response by glycocalyx. PBMC were stimulated with PHA (1 μg/ml) in the absence or in the presence of 10 to 100 μg of the indicated glycocalyx preparation per ml. The control is a solution of starch subjected to the same hot phenol extraction and processing as G2 (Westphal). Proliferation was determined by the uptake of tritiated thymidine after 5 days of culture. The percent inhibition is based on the proliferative response of PBMC cultured with PHA in the absence of glycocalyx (49,745 ± 3,160 cpm). The background proliferation of PBMC cultured without stimulus was 816 ± 168 cpm. The average results of triplicate cultures (± standard deviations) in a representative experiment are displayed. Similar results were obtained in 5 to 10 trials with each preparation.

RESULTS

The addition of *Staphylococcus* glycocalyx to cultures of PBMC inhibited the lymphocyte proliferative response to PHA (Fig. 1). In agreement with the data reported by Gray et al. (13), the inhibition was apparent 3 days after culture initiation and increased to 50 to 70% by the peak of the proliferative response (day 5). Proliferation of glycocalyx-inhibited PBMC cultures had decreased to background levels (<2,000 cpm) 7 days after culture initiation. This inhibitory effect was observed in >20 trials on PBMC collected from six different donors. This effect was observed with three or more different preparations of glycocalyx from each of three different staphylococcal isolates (three are displayed in Fig. 1). None of the preparations effected an inhibition of of the proliferative response that was greater than 70%. Hot phenol (Westphal) extraction of the G2-89 glycocalyx resulted in a fivefold reduction in protein content (Table 1) but did not reduce the inhibitory activity of the preparation (Fig. 1).

PBMC were depleted of adherent cells by incubation on plastic culture dishes as a first step in lymphocyte purification to address the question of whether the inhibitory activity of glycocalyx resulted from a direct effect on the T lymphocytes. However, upon testing for responsiveness to PHA and glycocalyx, it was found that these plastic-nonadherent cells were not sensitive to the inhibitory effects of glycocalyx (Table 2). The plastic-adherent monocytes, which were >90% $CD11a^+$ and <2% $CD2^+$, were therefore tested for their responsiveness to glycocalyx. Supernatants of monocytes cultured in medium alone, with 1 μg of LPS per ml, or with 100 μg of the glycocalyx preparations per ml were collected and assayed for PGE_2 by the radioimmunoassay and for IL1-β and TNF-α by the ELISA. All three

TABLE 2. Inability of glycocalyx to inhibit proliferation of monocyte-depleted PBMC[a]

Glycocalyx	[^{3}H]thymidine incorporation by PBMC (cpm ± SD)	
	Unseparated	Nonadherent
None	15,488 ± 1,922	10,524 ± 1,339
G-19-85	9,871 ± 1,139	12,767 ± 2,523
G-2-89	6,063 ± 1,202	12,503 ± 999
G-6-87	4,923 ± 197	11,351 ± 1,787

[a] PBMC with a normal monocyte component (unseparated PBMC) or PBMC depleted of plastic adherent monocytes (nonadherent PBMC) were cultured with PHA plus 100 μg of the indicated glycocalyx preparation per ml for 5 days. Averages of thymidine incorporation of triplicate cultures are displayed. Values for background incorporation by PBMC cultured without PHA were 887 ± 122 and 662 ± 112 cpm for unseparated PBMC and nonadherent PBMC, respectively.

glycocalyx preparations activated monocytes to produce significant ($P < 0.01$) amounts of PGE_2, IL-1β, and TNF-α, although the response was 5- to 10-fold lower than the monocyte response to *E. coli* LPS (Fig. 2). Similar results were obtained with the D10.G4 proliferation bioassay for IL-1 (21) and the L929 cytotoxicity assay for TNF-α (8). LPS stimulated >10-fold more IL-1 (116 U/ml) and TNF-α (15 U/ml) than did G-19-85, G-6-87, or G-2-89.

To determine whether glycocalyx stimulation of the adherent monocytes could result in secretion of a factor(s) that inhibited the proliferative response of the nonadherent fraction of PBMC, monocytes were incubated for 2 days with 100 μg of glycocalyx per ml, and the supernatant fluid was collected and tested for inhibitory activity on plastic-nonadherent PBMC. Although glycocalyx alone did not inhibit the proliferative response of nonadherent PBMC, the supernatants of cultures of glycocalyx-stimulated adherent monocytes did inhibit proliferation (Table 3). One of the mechanisms by which adherent monocytes could inhibit lymphocyte proliferation is by the elaboration of prostaglandins. The addition of 10^{-6} to 10^{-9} M PGE_2 to cultures of PBMC did inhibit the proliferative response to PHA, with a

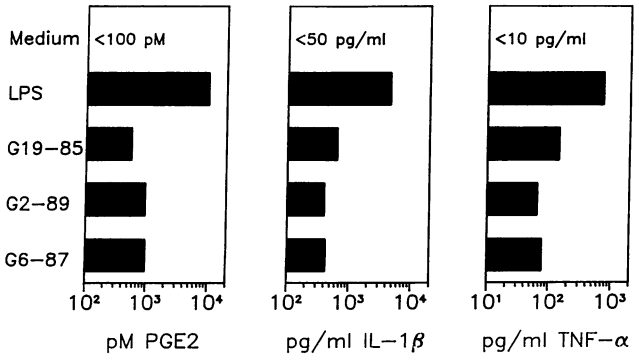

FIG. 2. Activation of adherent monocyte cytokine production by glycocalyx. Adherent monocytes from 4 × 10^5 PBMC were incubated overnight in 200 μl of complete medium without stimulus (medium), with the designated glycocalyx preparation (100 μg/ml), or with LPS (1 μg/ml). The culture supernatant was collected and assayed for PGE_2, IL-1β, and TNF-α as described in Materials and Methods. The results of all stimulated groups are significantly ($P < 0.01$) higher than those of the medium control. The results of all glycocalyx-stimulated groups are significantly ($P < 0.01$) lower than those of the LPS-stimulated group.

TABLE 3. Secretion of an inhibitor of lymphocyte proliferation by glycocalyx-stimulated monocytes

Inhibitor added to nonadherent PBMC	Stimulus added	[^{3}H]thymidine incorporated (cpm ± SD)
None	None	1,308 ± 292
None	PHA	23,671 ± 2,604
Glycocalyx	PHA	25,211 ± 1,917
CM (monocytes alone)	PHA	20,830 ± 2,050
CM (monocytes + glycocalyx)	PHA	12,462 ± 909
CM (monocytes + glycocalyx + indomethacin)	PHA	31,482 ± 4,187

[a] The conditioned medium (CM) was collected from cultures of plastic adherent monocytes after culture for 2 days without stimulus (monocytes alone), with 100 μg of glycocalyx per ml, or with 100 μg of glycocalyx per ml plus 1 μM indomethacin. Plastic nonadherent PBMC were then stimulated with PHA in the presence of 100 μg of glycocalyx per ml or in the presence of a 1:1 dilution of the conditioned medium. The average results of triplicate cultures are presented.

maximum inhibitory effect of 60 to 65% (Fig. 3). The radioimmunoassay of the supernatants of adherent monocytes revealed inhibitory levels ($\approx 10^{-9}$ M) of PGE_2 1 day after stimulation with 100 μg of glycocalyx per ml (Fig. 2). To determine whether PGE_2 release was the predominant mechanism by which the monocytes were inhibiting lymphocyte proliferative responses to PHA, the ability of indomethacin, an inhibitor of the cyclooxygenase pathway of prostaglandin synthesis, to prevent the inhibitory effect of glycocalyx was assessed. The addition of 10^{-6} M indomethacin to PHA-stimulated PBMC cultures prevented the inhibitory effect of glycocalyx on the proliferative response (Fig. 4), reducing the effect of G-19-85 from 33% inhibition to 34% enhancement, reducing the effect of G-6-87 from 51% inhibition to 14% enhancement, and reducing the inhibitory effect of G-2-89 from 52% to 6%. In contrast to the inhibitory activity displayed by supernatants of glycocalyx-stimulated monocytes, the supernatants of monocytes cultured with both glycocalyx and indomethacin displayed a costimulatory activity upon addition to cultures of PHA-stimulated nonadherent PBMC (Table 3). It should be noted that, although indomethacin effectively inhibited PGE_2 synthesis, indomethacin did not interfere with the ability of PGE_2 to inhibit proliferative responses of PBMC, did not interfere with the

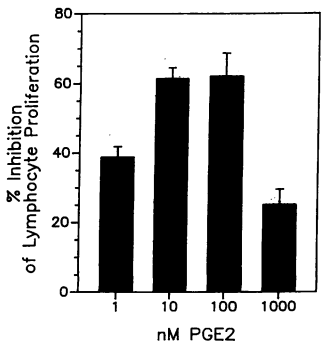

FIG. 3. Inhibition of PBMC proliferation by PGE_2. PBMC were stimulated with PHA in the presence of 1 to 1,000 nM PGE_2. The percent inhibition of proliferation is based on the proliferative response of PBMC stimulated in the absence of added PGE_2 (40,434 ± 3,403 cpm). Background proliferation of unstimulated PBMC was 1,181 ± 113 cpm. The average results of triplicate cultures (± standard deviations) are displayed.

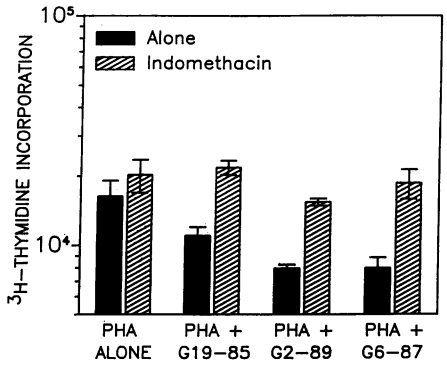

FIG. 4. Reversal of the inhibitory effect of glycocalyx by indomethacin. PBMC were stimulated with PHA in the presence of the indicated preparation of glycocalyx with or without addition of 1 μM indomethacin. Proliferative responses were assayed by measuring [^{3}H]thymidine incorporation after 5 days of incubation. The average results of triplicate cultures (± standard deviations) are displayed. The background proliferation of unstimulated PBMC was 1,892 ± 422 cpm.

ability of supernatants of glycocalyx-stimulated monocytes to inhibit proliferative responses of PBMC, and did not, by itself, augment the responses of plastic-nonadherent PBMC (data not shown).

DISCUSSION

The role of bacterial glycocalyx in the pathogenesis of prosthesis-associated infections has become a focus of attention with recent demonstrations of its role in colonization of bone (19, 20, 25, 28) and prosthetic devices (11, 23, 24, 27) and in protecting bacteria from surfactants (12), antibodies (3), antibiotics (5), and phagocytosis (10, 16, 34, 39). It has also been suggested that *S. epidermidis* glycocalyx may inhibit immune responses to the bacteria by directly interfering with T-lymphocyte activation (13, 30). The data presented in the current report demonstrate that glycocalyx preparations from *S. epidermidis* and from *S. lugdunensis* do not have a direct inhibitory effect on T-cell activation. However, the glycocalyx does appear to affect monocyte function, stimulating monocyte production of PGE_2 and thereby reducing T-lymphocyte proliferative responses. That monocyte-derived PGE_2 is the predominant mediator of the antiproliferative effect of glycocalyx on T lymphocytes is supported by the demonstrations that (i) glycocalyx stimulates PGE_2 secretion by monocytes; (ii) indomethacin, an inhibitor of PGE_2 synthesis, abrogates the inhibitory effect of glycocalyx on PBMC and prevents the production of the inhibitory factor by monocytes; and (iii) PGE_2 exerts a similar inhibitory effect on lymphocyte proliferative responses (Fig. 3) (29, 35, 40).

The data presented in the current report demonstrate that glycocalyx preparations from two different strains of *S. lugdunensis* and one strain of *S. epidermidis* that were isolated from clinical specimens displayed the ability to inhibit lymphocyte proliferative responses via stimulation of monocyte PGE_2 production. All of the strains were pathogenic in a murine model of foreign body infections (18). Analysis of the general composition of the glycocalyx preparations revealed significant amounts of both proteins and carbohydrates as well as phosphates, which may reflect the presence of teichoic acid (14, 36). Coagulase-negative staphylococci do produce a variety of exoproteins such as α- and

δ-hemolysins, DNase, and proteases. These do not appear to play a dominant role in the inhibitory activity of the glycocalyx, since *S. lugdunensis* 6-87 and 2-89 do not elaborate detectable amounts of these exoproteins (18), yet glycocalyx preparations from these strains were effective inducers of monocyte PGE_2 production. In addition, depletion of protein by hot phenol extraction did not reduce the ability of the glycocalyx preparations to induce monocyte PGE_2 production and to inhibit proliferation of PHA-stimulated PBMC. These observations suggest that the activity may be due to polysaccharide or teichoic acid components of the glycocalyx. Attempts to identify and purify the active component(s) are currently in progress.

The endotoxin of gram-negative bacteria is known to stimulate monocytes. However, endotoxin contamination of the glycocalyx preparations is not likely to be responsible for the observed effects, because (i) control preparations of starch, generated simultaneously with glycocalyx preparations under the same endotoxin-free conditions, were inactive; (ii) glycocalyx preparations contained negligible levels (<0.1 ng/100 μg) of endotoxin according to the *Limulus* assay; and (iii) the addition of endotoxin (*E. coli* O11:B4-W) to PBMC cultures at levels 10- to 100-fold higher (1 ng/ml) than the maximum possible endotoxin contamination of glycocalyx did not result in detectable inhibition of the proliferative response of the PBMC to PHA (data not shown).

Several recent studies have indicated that microorganisms produce several different bioactive factors that stimulate macrophages (32, 33, 37). These factors share with glycocalyx the characteristic of being implicated in macrophage-mediated immunosuppression. Oligosaccharides and polysaccharides from bacteria and yeast cells, free of the classical gram-negative endotoxins, have been reported to reduce immunoproliferative responsiveness of T lymphocytes by stimulating suppressive activity in macrophages (32, 33). Immunosuppression during treponeme infections has been shown to result from prostaglandin production by treponeme-stimulated macrophages (37). It has been reported that a component or components of bacterial glycocalyx may directly inhibit some granulocyte functions such as the response to chemotactic gradients, oxidative burst, and engulfment of particles (10, 16, 30, 34, 39). The current study indicates that the glycocalyx of coagulase-negative staphylococci does contain a component(s) that is capable of activating monocytes. This activation results not only in PGE_2 production but also in IL-1 and TNF-α production and secretion. IL-1 and TNF-α, like PGE_2, play significant roles in acute inflammatory responses (4, 7). How glycocalyx could be of such apparent benefit to coagulase-negative staphylococci in the establishment of foreign body infections while stimulating monocytes to secrete inflammatory cytokines represents a fascinating paradox. Molecular identification and characterization of the components of glycocalyx that interact with macrophages and neutrophils may lead to a resolution of this paradox.

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